WHO recommendation on surfactant replacement therapy for newborns with respiratory distress syndrome

17 November 2015

Recommendation
Surfactant replacement therapy is recommended for intubated and ventilated newborns with respiratory distress syndrome.

(Conditional recommendation [only in health-care facilities where intubation, ventilator care, blood gas analysis, newborn nursing care and monitoring are available] based on moderate-quality evidence).

Publication history
First published: November 2015
Updated: No update planned
Assessed as up-to-date: November 2015

Remarks
- The GDG members were of the opinion that the benefits of the intervention in reducing mortality clearly outweighed the possible increased risk of pulmonary haemorrhage.
- The recommendation should be used in higher-level health-care facilities because it applies to preterm newborns with respiratory distress syndrome who have access to intubation and mechanical ventilation.
- In high-income countries, surfactant treatment may reduce overall hospital costs, but this might not be the case in low- and middle-income countries (LMICs).
- In many LMICs, resource implications (both human and material) may make the use of surfactant a lower priority.

Background
Preterm birth, defined as birth before 37 weeks of gestation, is the single most important determinant of
adverse infant outcomes, in terms of survival and quality of life. (1) Globally, it is the leading cause of
perinatal and neonatal mortality and morbidity. (2) Preterm infants are particularly vulnerable to
complications due to impaired respiration, difficulty in feeding, poor body temperature regulation and high
risk of infection. (3-5) With the increasing contribution of neonatal deaths to overall child mortality, it is
critical to address the determinants of poor outcomes related to preterm birth to achieve further reductions in
child mortality. (6-8)

Infant mortality and morbidity from preterm birth can be reduced through interventions delivered to the
mother before or during pregnancy, and to the preterm infant after birth. (9) Interventions can be directed at
all women for primary prevention and reduction of the risk of preterm birth (e.g. smoking cessation
programme) or aimed at minimizing the risk in women with known risk factors (e.g. progestational agents,
cervical cerclage). (10) However, the most beneficial set of maternal interventions are those that are aimed at
improving outcomes for preterm infants when preterm birth is inevitable (e.g. antenatal corticosteroids,
magnesium sulfate and antibiotic prophylaxis). (9) Special care of the preterm newborn to prevent and treat
complications of prematurity is also critical to newborn survival. In high-income countries, reductions in
mortality rates in infants that were born preterm have been driven largely by improved care and, more
importantly, by appropriate policy changes.

Methods

The recommendations were developed using standard operating procedures in accordance with the process
described in the WHO handbook for guideline development (11). Briefly, these included (i) identification of
priority questions and critical outcomes, (ii) retrieval of the evidence, (iii) assessment and synthesis of
evidence, (iv) formulation of recommendations, and (v) planning for the dissemination, implementation,
impact evaluation and updating of the guideline.

The scientific evidence underpinning the recommendations was synthesized using the Grading of
Recommendations Assessment, Development and Evaluation (GRADE) approach (12). Up-to-date
systematic reviews were used to prepare evidence profiles for the priority questions. WHO then convened a
Technical Consultation in May 2014 where an international group of experts – the Guideline Development
Group (GDG) – formulated and approved the recommendations based on the evidence profiles.

In November 2014, an online consultation of the GDG was conducted to review and revise the
recommendations in the light of the findings of a large implementation trial of antenatal corticosteroids in
low-resource countries.

Further information on procedures for developing this recommendation are available here.

Recommendation question

For this recommendation, we aimed to answer the following question:

- In newly born preterm babies who have or are at risk of respiratory distress syndrome (P), is surfactant
  therapy (I), compared with routine care without surfactants (C), effective in reducing adverse newborn
  outcomes (O)? If so:
  - How early should the surfactant therapy be started?
  - Should surfactants be given for prophylaxis in newborns where respiratory distress syndrome
    has not yet set in, or selectively when existing respiratory distress is worsening?
  - Which types of surfactant are effective – animal-derived or synthetic; protein-containing or
Evidence summary

Surfactant replacement therapy (SRT) for preterm neonates with clinical and/or radiologically established respiratory distress syndrome (RDS)

Two Cochrane reviews that evaluated the effects of SRT on neonatal mortality and morbidity provided evidence for this recommendation. The first, by Seger et al. (13), evaluated the effects of the use of animal-derived surfactants, whilst the second, by Soll (14), focused on the use of protein-free synthetic surfactants; both reviews included studies that compared the treatment to placebo or no treatment.

An updated search conducted for both reviews found no additional relevant studies. All included studies were conducted in intensive care units within hospitals in HICs. The interventions included the administration of a single dose or multiple doses of exogenous animal-derived or synthetic surfactants by endotracheal tube for babies with clinical or radiological features of RDS. The comparison groups included babies receiving placebo or no treatment. The results of the two Cochrane reviews were not pooled because of the differences in the source of the surfactants used (animal-derived versus synthetic) and because protein-free synthetic surfactants are no longer commercially available in most countries.

Animal-derived surfactants

The review by Seger et al. (13) included 13 RCTs in which preterm neonates with clinical or radiological evidence of RDS were either treated with surfactants from bovine, porcine or amniotic fluid sources or received no surfactant therapy.

**Neonatal death:** SRT using animal-derived surfactants was found to be associated with lower overall and in-hospital neonatal mortality. Ten trials involving 1469 preterm babies showed a 32% lower risk of overall neonatal mortality, compared with no SRT (19.5% versus 28.4%; RR 0.68, 95% CI 0.57–0.82). SRT with animal-derived surfactants also showed a 37% lower risk of in-hospital neonatal mortality compared with controls (RR 0.63, 95% CI 0.44–0.90; 7 studies, 421 neonates).

**Severe neonatal morbidity:** Animal-derived surfactant for SRT was associated with a 53% reduction in the risk of air leaks as compared to no surfactant (14.7% versus 31.0%; RR 0.47, 95% CI 0.39–0.58; 7 studies, 1380 neonates). However, no significant differences in the effects on the risks of sepsis (RR 1.14, 95% CI 0.87–1.48), pulmonary haemorrhage (RR 1.29, 95% CI 0.77–2.15), BPD (RR 0.95, 95% CI 0.84–1.08) or severe IVH (RR 0.93, 95% CI 0.79–1.10) were observed between those receiving SRT versus no SRT.

Protein-free synthetic surfactants

In the review by Soll (14), six trials that compared protein-free synthetic surfactants for SRT with no SRT were included. Five of these trials used a surfactant formulation whose production has been discontinued and the other used dry 1, 2-dipalmitoyl-sn-glycero-3-phosphocholine and phosphatidylglycerol preparation.

**Neonatal death:** Six trials involving 2352 preterm neonates showed that SRT using synthetic surfactants was associated with a 27% lower risk of overall neonatal death when compared to no SRT (RR 0.73, 95% CI 0.61–0.88). These results also demonstrated a 21% lower risk of in-hospital neonatal mortality (RR 0.79, 95% CI 0.68–0.92).
Severe neonatal morbidity: Five trials showed that SRT using synthetic surfactants resulted in a significant 36% lower risk of air leaks (RR 0.64, 95% CI 0.55–0.76; 2328 neonates) and a 25% lower risk of BPD (RR 0.75, 95% CI 0.61–0.92; 2248 neonates). However, synthetic surfactant therapy was not associated with a significantly lower risk of severe IVH when compared to no SRT (RR 0.84, 95% CI 0.63–1.12; 2328 neonates).

Further information and considerations related to this recommendation can be found in the WHO guidelines, available at:

http://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1

http://apps.who.int/iris/bitstream/handle/10665/183038/WHO_RHR_15.17_eng.pdf?sequence=1

Implementation considerations

- The successful introduction of this recommendation into national programmes and health-care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols based on this recommendation.
- The recommendation should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. Any changes should be made in an explicit and transparent manner.
- A set of interventions should be established to ensure that an enabling environment is created for the use of the recommendations, and that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice.
- In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged.

Research implications

The GDG identified that further research on the following high-priority questions is needed:

- What is the efficacy of surfactants in a context where antenatal corticosteroids and early CPAP is provided (without immediate obligatory mechanical ventilation) for babies who are at risk of respiratory distress syndrome (e.g. InSURE – intubation, surfactant replacement therapy and extubation)?

Related links


Supporting systematic reviews:


Other links of interest

Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors

Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice

WHO Programmes: Sexual and Reproductive health

Maternal Health

Infant, Newborn Health

References


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